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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/762,566 | 01/23/2004 | Richard Franklin | 20342/1202529-US1 | 3220 |

7278 7590 04/19/2007

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| EXAMINER | |
|---|---|
| HUGHES, ALICIA R | |
| ART UNIT | PAPER NUMBER |
| 1614 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/19/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/762,566 | FRANKLIN, RICHARD | |
| | Examiner | Art Unit | |
| | Alicia R. Hughes | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-34,37,38,43,45,46 and 49* is/are pending in the application.

4a) Of the above claim(s) *10,11,16,38,43,45,46 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-9,12-15,17-26-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Claims*

Claims 2-34,37,38,43,45,46 and 49 are pending. Of the forementioned claims, claims 10,11,16,38,43,45 and 46 and 49 are withdrawn from consideration, being the subject of a non-elected invention. Applicant cancelled claims 1, 35, 39-42, 44, and 47-48 in their response filed on 19 March 2007, leaving claims 2-9,12-15,17-26-34 and 36 as the subject of examination in this Office Action.

### *Objections*

The disclosure is objected to because of the following informality: the presence of a legend to Figure 1 is improper.

### *Claim Rejection - 35 U.S.C. §112.1*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-9,12-15,17-26-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 2 is enabled for the treatment of thrombocythemia and more particular, essential thrombocythemia by means of administration of an effective amount of anagrelide or an

anagrelide salt transdermally. However, the claimed prophylaxis of thrombocythemia is not supported by the specification. As a result, the effect of performing the invention by one skilled in the art would be that of undue experimentation.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in organic chemistry is high, the results of experiments to discover treatments for the illnesses and conditions recited in claim 2, is unpredictable. While all of the Wands factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The applicant has provided a number of working examples for producing transdermal devices for the delivery of anagrelide and/or anagrelide salts. And further, Applicant has also referenced examples of tests to support the bioavailability of anagrelide as a result of transdermal deliver. However, the applicant has failed to enable the prevention of thrombocythemia noted in the claimed invention through the examples provided. Prophylaxis is generally defined as "the preventing of disease." Random House Unabridged Dictionary, Random House, Inc. 2006.

While there is support for the treatment of thrombocythemia, the specification is void of support for the prevention of thrombocythemia.

As such, the art of the claimed invention lacks predictability because the claim as written to include prevention of thrombocythemia is drawn too broadly.

## *Claim Rejections – 35 U.S.C. §102(b)*

The following is a quotation of 35 U.S.C. §102(b), which forms the basis for all obviousness rejections set forth in this Office Action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

For the purpose of examination herein, the pending claims are given their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). Limitations appearing in the specification but not recited in the claim should not be read into the claim. *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) (claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily). *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969).

Claim 2 is rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 6,156,753 [hereinafter referred to as "Doherty, Jr., et al"] in light of U.S. Patent No. 6,024,975 [hereinafter referred to as "D'Angelo et al"].

Doherty et al teach the transdermal administration of anagrelide (Col. 18, lines 24-39, cls. 1-3) It is understood that the properties of an already known compound are inherent, namely treating thrombocythemia with anagrelide is inherent. Thus, Applicant has elucidated an inherent biochemical mechanism regarding the administration of anagrelide. More specifically,

a chemical composition and its properties are inseparable. In re Papesch, 315 F. 2ed 381 (CCPA 1963). Therefore, if the prior art teaches the identical chemical structure, the properties the Applicant discloses or claims are necessarily present, making the invention either obvious or anticipated. *See In re Best*, 562 F. 2d 1252, 1255 (CCPA 1977).

D'Angelo et al teach that drugs administered via transdermal delivery "are not subject to liver metabolism" (Col. 1, lines 23-29). In accordance with the Manual of Patent Procedure §2131.01, a secondary reference may be cited for a rejection made under 35 U.S.C. §102 so long as the reference is cited to show that a characteristic not disclosed by the primary reference is inherent or necessarily present, making the application of D'Angelo proper in this rejection.

In light of the foregoing, a method of preventing thrombocythemia by transdermal administration of anagrelide is clearly anticipated.

***Claim Rejections – 35 U.S.C. §103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-9, 12, and 17-20, 26-27, 32 and 36 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,194,420 [hereinafter referred to as "Lang"], in view of U.S. Patent No. 6,221,383 [hereinafter referred to as "Miranda et al"], and in further view of D'Angelo et al.

Lang teach a pharmaceutical composition comprising anagrelide or anagrelide-type compounds with a pharmaceutically acceptable excipient to be utilized in the treatment of essential thrombocythemia (Abstract; Col. 1, lines 1-36 and Col. 2, lines 36-40).

One of ordinary skill in the art would be motivated to combine the teachings of Lang with the teachings Miranda et al, because they teach overlapping subject matter, the administration of anagrelide as part of a pharmaceutical composition.

Miranda et al teach that "known delivery systems involve incorporation of a medicament into a carrier such as a polymeric matrix" (Col. 1, lines 29-30) and that the transdermal drug delivery system may comprise a monolithic adhesive matrix device and furthermore, may "include a backing material and a release liner as known in the art" (Col. 4, lines 34-36). Furthermore, a preferred embodiment of the invention is a multiple polymer adhesive system that contains an acrylic polymer ... or acrylic adhesive (Col. 9, line 32).

Miranda et al also teach that drugs that can be administered pursuant to their invention include menthol and anagrelide (Col. 11, lines 58-60; Col. 24, line 6; and Col. 25, line 56) and that the surface area ranges from 1 to 200 square centimeters (Col 36, lines 11-15).

One of ordinary skill in the art would be motivated to combine the teachings of D'Angelo et al with the teachings of Lang and Miranda et al, because when the teachings of Lang and Miranda et al are combined they overlap with D'Angelo in subject matter, most notably administration of medicaments, particularly anagrelide, by transdermal delivery.

D'Angelo et al teach transdermal delivery of drugs in connection with patch systems (Col. 1, lines 17-20). They specifically teach that "[s]kin drugs which are administered through the skin are not subject to liver metabolism" (Col. 1, lines 26-28). D'Angelo et al also teach

[t]he chemical system is preferably administered via a multidose transdermal patch assembly which includes a drug-impervious support impressed to form a series of compartments. Each compartment is a reservoir for a unit dose of a drug active to be transdermally administered" (Abstract). They also teach that "[t]he individual enclosing devices are movable to release the unit dose into contact with the skin of the patient and are actuable to control the transdermal absorption of the drug actives" (Abstract; see also Col. 4, lines 19-27), contain skin enhancers (Col. 4, line 18) and that "[t]he drugs and their adjurants are dissolved, suspended, absorbed or contained in matrices or solutions" (Col. 4, lines 59-62).

In light of the foregoing, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of Lang, Miranda et al, and D'Angelo to conclude that the combination of anagrelide or its salt form, along with a skin permeation enhancer, administered transderally so as to avoid the first pass liver metabolism would be effective in the treatment of essential thromboycythemia.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art that the administration of a single or multiple layer formulation of an effective amount of anagrelide or an anagrelide salt and a menthol acting has a skin permeation enhancer with acrylic adhesive with a surface area ranging from 1 to 200 square centimeters acting together as a transdermal delivery device would be effective for treating essential thrombocythemia.

Claims 21-23 and 28-31 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,194,420 [hereinafter referred to as "Lang"] in view of U.S. Patent No. 6,024,975 [hereinafter referred to as "D'Angelo et al"] and in further view of U.S. Patent No. 5,133,972 [hereinafter referred to as "Ferrini et al"].

The teachings of Lang and D'Angelo et al, *supra*, are incorporated herein by reference. One of ordinary skill in the art would be motivated to combine the teachings of Lang and D'Angelo et al with the teachings of Ferrini et al, because each contains overlapping subject matter, most notably administration of medicaments, by transdermal delivery.

Ferrini et al teach a multilayered therapeutic system for the transdermal administration of an active ingredient, wherein the system consists essentially of: (a) a closed backing foil that is impermeable to subsequent layers of constituents of the active ingredient formulation; (b) a reservoir for the active ingredient that is next to the backing foil, if the active ingredient is not already present in the adhesive foil; (c) an adhesive layer; and (d) a peel-off protecting foil (Col. 10, lines 3-17). The backing foil consists of materials that are impermeable to constituents contained in the reservoir (Col. 10, lines 38-41). The reservoir holds the active ingredient and is generally situated between the backing foil and adhesive layer, which is in turn arranged on the peel-off protecting foil (Col. 10, lines 52-56). Importantly, the reservoir may hold a liquid, semi-solid, or solid active ingredient and may form as a homogenous or inhomogenous polymer matrix containing itself and the active ingredients (Col. 10, lines 56-62). The reservoir can also hold a penetration enhancer, especially ethanol, with the active ingredient (Col. 11, lines 58-62).

Ferrini et al teach that in addition to the active ingredient and penetration enhancer, reservoir contents of a transdermal patch can also contain propylene glycol and water (Col. 11, lines 53-56). By way of example, Ferrini et al also teach a membrane transdermal system wherein the system contains 10 parts of an active ingredient, 84 parts ethanol, 5 parts azone, 3 parts Klucel HF. However, the neither the reference nor the combined references teach specifically, the combination containing, exclusively: (1) the active ingredient, azone, ethanol,

water, propylene glycol, and Klucel HF; or (2) the active ingredient, ethanol, and Klucel HF. However, the use of these excipients individually are well-known to skilled artisans.

As a matter of law, "[i]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie obvious*.). *See also In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious).

Under the law also, a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of" having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.). Such is the case between the taught referenced and the claimed invention herein. As stated herein prior, Ferrini et al teach

that in addition to the active ingredient and penetration enhancer, reservoir contents of a transdermal patch can also contain propylene glycol and water (Col. 11, lines 53-56). By way of example, Ferrini et al also teach a membrane transdermal system wherein the system contains 10 parts of an active ingredient, 84 parts ethanol, 5 parts azone, 3 parts Klucel HF. While the proportions taught by Ferrini et al are not total within the range of the disclosed invention, they are close enough that one of skill in the art would expect them to have the same properties.

Applicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir.1990).

In the absence of a showing that the ranges claimed in the instant matter are critical to the optimal performance of the invention, it would have been *prima facie* obvious to one of ordinary skill in the art to combine Klucel HF, polyethylene glycol, azone, ethanol and/or water with anagrelide in a transdermal delivery system to be administered to treat thrombocythemia and more particularly, essential thrombocythemia.

Claims 13-15, 24-25 and 33-34, and 36 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,194,420 [hereinafter referred to as "Lang"] in view of U.S. Patent No. 6,024,975 [hereinafter referred to as "D'Angelo et al"]. and in further view of U.S. Patent No. 4,847,276 [hereinafter referred to as "Yarrington"].

The teachings of Lang and D'Angelo et al, *supra*, are incorporated herein by reference. One of ordinary skill in the art would be motivated to combine the teachings of Lang and D'Angelo et al with the teachings of Yarrington, because each contains overlapping subject matter, most notably treatment of a myeloproliferative disease, particularly essential thrombocythemia.

Yarrington teach the treatment of thrombocythemia by the administration of 0.25 to 50 mg/kg/day of an active compound (Col. 6, lines 12-20 and 30-32, Cls. 9,10, and 13). Yarrington also teach the administration of 1.5 to 4.0 mg of anagrelide per day, with reasonable effectiveness of the drug evident after five days of administration (Col. 2, lines 9-14).

In view of the foregoing, it would have been *prima facie* obvious to one of ordinary skill in the art that the administration of 0.1 to 20 mg/kg/day of anagrelide and more particularly, 0.5 to 3 mg of anagrelide daily for at least 1 to 7 days via transdermal delivery would effectively treat essential thrombocythemia.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 A.M. until 5:00 P.M. on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application is proceeding is assigned 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

17 March 2007
ARH

BRIAN-YONG S. KWON
PRIMARY EXAMINER